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Association between advanced glycation end-products and functional performance in Alzheimer's disease and mixed dementia

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ABSTRACT

Background: People with Alzheimer's disease (AD) experience, in addition to the progressive loss of cognitive functions, a decline in functional performance such as mobility impairment and disability in activities of daily living (ADL). Functional decline in dementia is mainly linked to the progressive brain pathology. Peripheral biomechanical changes by advanced glycation end-products (AGEs) have been suggested but have yet to be thoroughly studied.

Methods: A multi-center, longitudinal, one-year follow-up cohort study was conducted in 144 people with early stage AD or mixed Alzheimer's/Vascular dementia. Linear mixed model analyses was used to study associations between AGE-levels (AGE reader) and mobility (Timed Up and Go), and ADL (Groningen Activity Restriction Scale and Barthel index), respectively.

Results: A significant association between AGE levels and mobility ($\beta = 3.57$, 95%CI: 1.43–5.73) was revealed; however, no significant association between AGE levels and ADL was found. Over a one-year time span, mean AGE levels significantly increased, and mobility and ADL performance decreased. Change in AGE levels was not significantly correlated with change in mobility.

Conclusions: This study indicates that high AGE levels could be a contributing factor to impaired mobility but lacks evidence for an association with ADL decline in people with early stage AD or mixed dementia. Future research is necessary on the reduction of functional decline in dementia regarding the effectiveness of interventions such as physical activity programs and dietary advice possibly in combination with pharmacologic strategies targeting AGE accumulation.

Key words: Alzheimer's disease, dementia, functional mobility, activities of daily living, biomarker, advanced glycation end-products

Background

People with Alzheimer's disease (AD) experience, in addition to the progressive loss of cognitive functions, a decline in functional performance such as mobility impairment and disability in activities of daily living (ADL) (American Psychiatric Association, 1994). In early stage AD, there are already decreases in step length and walking velocity and, in early vascular dementia (VaD), a small step gait,

slow stepping, ataxic gait, and unsteadiness is found (Scherder *et al.*, 2011). Impairment in basic ADL (BADL) functions (i.e., bathing, toileting, feeding, and dressing) in early dementia is more reliant on decline in motor function, whereas impairment in instrumental ADL (IADL) functions (i.e. housekeeping, cooking and finance management) is more reliant on cognition decline (Martyr and Clare, 2012). Furthermore, it is known that specifically in the early stages initiating certain IADL (i.e. preparing a meal, finance management) is found to be more strongly impaired than their performance (Giebel *et al.*, 2017). Decline in functional performance contributes to an increase in care burden and a decrease in the quality

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of life (Andersen *et al.*, 2004). Lower level and accelerated decline of functional performance is suggested to predict the subsequent development of mild cognitive impairment and AD and can precede cognitive impairment by several years (Buchman and Bennett, 2011). Ramakers *et al.* determined that, even five years prior to the dementia diagnosis, walking impairments were significantly higher in pre-clinical people with dementia compared to the control group (Ramakers *et al.*, 2007). A decline in functional performance could be predicted with biomarkers; one of the proposed biomarkers is advanced glycation end-products (AGEs). AGE accumulation contributes to the age-related decline of the functioning of cells and tissues in normal aging (Rahmadi *et al.*, 2011). Interestingly, AD is related to higher concentrations of AGEs (Rahmadi *et al.*, 2011; Li *et al.*, 2012). AGEs, therefore, are a potential biomarker and an accompanying risk factor for the decline of functional performance in people with AD and mixed dementia (AD/VaD).

Advanced glycation end products

Decline in functional performance in dementia is primarily associated with central mechanisms as a result of progressive brain pathology. Peripheral biomechanical changes have been suggested but have yet to be thoroughly studied. Studies in stroke patients show that immobility is associated with adaptive mechanical and morphological changes in muscle tissue in which muscles become stiffer (Farmer and James, 2001). A review comprising eight studies suggests that, in participants without dementia, AGEs-induced muscle biomechanical changes contribute to a decline in walking abilities and in BADL as well as physical frailty (Drenth *et al.*, 2016). It was recently found that AGEs are associated with the presence and severity of paratonia, a distinctive form of hypertonia/movement stiffness in dementia, which suggests that peripheral biomechanical changes contribute to movement stiffness in early stage dementia (Drenth *et al.*, 2017).

AGEs are formed by the non-enzymatic condensation of a reducing sugar with proteins or lipids and accumulate in hyperglycaemic environments. The accumulation of AGEs is an element of normal metabolism that accelerates in a wide variety of diseases and during normal aging (Ahmed and Thornalley, 2007; Rahmadi *et al.*, 2011). AGEs can be categorized into fluorescent cross-linking, non-fluorescent cross-linking, fluorescent non-crosslinking, and non-fluorescent non-crosslinking (Meerwaldt *et al.*, 2004). AGEs tissue accumulation can be estimated non-invasively by skin auto-fluorescence (SAF) with an AGE reader

by utilizing the fluorescent properties of specific AGEs that correlate with non-fluorescent AGEs (Meerwaldt *et al.*, 2004).

The cross-linking of long-lived proteins, particularly collagen, is responsible for increasing mechanical stiffness and loss of elasticity (Avery and Bailey, 2005). Non cross-linking effects occur by the binding of AGEs to the receptor for AGEs (RAGE) that incites the production of pro-inflammatory cytokines and free radicals. At the central level, interaction between AGEs, Amyloid-beta, and tau-protein have been ascertained to affect neuronal function (Ahmed and Thornalley, 2007). At the peripheral level, this AGE/RAGE interaction affects collagen tissue and may play a role in sarcopenia (loss of muscle mass and strength) through upregulated inflammation and endothelial dysfunction in the intra-muscular microcirculation (Payne, 2006).

These peripheral and central effects of AGEs may have a direct or indirect influence on muscle function and functional performance decline; however, this has not been studied in people with dementia. Early detection could initiate interventions targeting AGE accumulation, such as physical activity programs and dietary advice possibly in combination with pharmacologic strategies (Magelhaes *et al.*, 2008; Puyvelde *et al.*, 2014; Nenna *et al.*, 2015) to attenuate functional decline, affording people with dementia longer independence. The aim, therefore, was to investigate the association between AGEs and functional performance in people with AD and mixed dementia (AD/VaD).

Method

Design

The study was designed as a multi-center, longitudinal, one-year observational follow-up cohort study with three assessments: at baseline, after six months, and after 12 months.

Study population

Participants, selected from 24 dementia day-care centers in the Netherlands, were considered to be eligible for inclusion when they satisfied four criteria: (1) an established diagnosis of Alzheimer's disease (AD) or mixed Alzheimer's/Vascular dementia (AD/VaD) according to DSM-IV criteria (American Psychiatric Association, 1994); (2) a score of stage five or lower on the Global Deterioration Scale (GDS) (Reisberg *et al.*, 1982); (3) able to walk 10 m (a walking aid was allowed); and (4) having a light-colored (Caucasian) skin

due to the limitations of the AGE-reader device (Meerwaldt *et al.*, 2004). Written informed consent was obtained from the participants or their legal representatives. The medical ethical committee of the University Medical Centre Groningen approved the study (NL43641.042.13).

Design and study population are derived from the PARAGE study (Drenth *et al.*, 2017) and described more extensively.

Outcome measures

MOBILITY

The participant's functional mobility was assessed with the Timed Up and Go (TUG). It measures the amount of time a participant takes to stand up from a chair (with an approximate height of 46 cm) and walk 3 m, and then turn around a cone, walk back to the chair, and sit down. The TUG is a validated and reliable test for people with dementia. A score of 20 sec or more indicates the presence or increase of additional mobility problems (Ries *et al.*, 2009). TUG measurements were obtained by experienced physiotherapists followed by the AGEs measurements assessed by the main researcher at each visit. Prior to the study, the physical therapists were trained by the main researcher on how to perform the measurements.

ADL

To assess the broad construct of ADL, the outcome from the participants' perspectives is measured with the Groningen Activity Restriction Scale (GARS) (Kempen *et al.*, 1993) and from the day-care center staffs' perspective with the Barthel index (BI) (Collin *et al.*, 1988). The GARS has been ascertained as being valid for measuring disabilities in personal care. With the GARS, the participants are questioned about their capabilities in personal care on two subscales. The first subscale is regarding BADL (11 items), and the second subscale relates to IADL (7 items). The answers are rated on a four-point scale with 1 meaning no support and 4 meaning only with help. A lower score on the combined subscales indicates more ADL independence with 18 as the minimum score (Metzelthin *et al.*, 2010). The BI is a valid and reliable measurement for assessing a person's ability of self-care. Ten items regarding BADL and mobility are rated by the participant's caregiver based on the amount of assistance required to complete each activity. A higher score indicates more BADL independence with 20 as the maximum score (Collin *et al.*, 1988). The questionnaires (GARS and BI) were administered by key staff personnel from the day-care centers within the same week that the AGEs

measurements were taken. Before the study, the participating day-care staff was trained by the primary researcher to perform the measurements.

AGE LEVEL

AGE levels are measured with the AGE reader (Diagnostics, Groningen, the Netherlands) that is a desktop device measuring fluorescent skin AGEs and is reported to be valid and reliable for the quantification of AGEs tissue accumulation (Meerwaldt *et al.*, 2004). The skin of the forearm is illuminated by a light source in the AGE reader through a 1-cm² hole that is guarded against surrounding light. Excitation light in the wavelength range of 300–420 nm (peak excitation ~350 nm) is projected onto the skin surface. The intensity of light emitted from the skin in the wavelength range of 420–600 nm is measured with a spectrometer. SAF is calculated as the ratio between the emission light and the excitation light using the AGE reader software and expressed in arbitrary units (AU). A high SAF score corresponds to a high tissue AGEs level (Meerwaldt *et al.*, 2004). The measurements were performed on the forearm without sweat, skin lotions, or visible skin abnormalities and with the assessor being blinded for functional performances scores. All AGE reader measurements were performed at room temperature in a standardized semi-dark environment with the participants in a seated position and the volar side of the right forearm placed on top of the AGE reader. The mean of three consecutive measurements was used for analysis.

OTHER VARIABLES

Dementia characteristics were provided by the general practitioner (GP) or the local physician. Cognitive functioning was measured by experienced psychologists or physicians with the Mini-Mental State Examination (MMSE). The MMSE is an 11-item questionnaire with a maximum score of 30, which indicates no cognitive decline, and a minimum score of 0, which indicates a very severe cognitive decline (Folstein *et al.*, 1975). Dementia severity was categorized by key staff personnel from the day-care centers using the GDS that identifies seven clinically recognizable stages from normal (no dementia) to severe dementia (Reisberg *et al.*, 1982). Paratonia was diagnosed by physical therapists with the Paratonia Assessment Instrument (PAI) at each visit. The PAI is a reliable and valid dichotomous assessment instrument with which an examiner can establish the presence (or absence) of paratonia by successively moving all four limbs passively in flexion and extension, while

the participant is in a sitting position (Hobbelen *et al.*, 2008).

The use of medication and the presence of comorbidities (ICD-9 classification) were retrieved from the participant's medical records and GP files. The use of five or more medications was labeled as polypharmacy (World Health Organisation, 2014).

Statistical analyses

SAMPLE SIZE CALCULATION

A mixed model sample size calculation (Liu and Liang, 1997) was based upon a 0.5 correlation between repeated measurements, 0.3 variance of the random intercept, 0.3 residual variance, a true effect size of 0.5, a desired power of 80%, and a two-sided alpha of 0.05. This resulted in a total sample size of 152. Addressing an eventual 10% withdrawal resulted in a required total number of approximately 165 participants. Baseline characteristics are depicted by descriptive statistics and presented in Table 1.

ASSOCIATION BETWEEN AGE LEVELS AND MOBILITY AND ADL

To investigate the association between AGE levels on mobility and ADL (BADL/IADL), linear mixed model analyses (LMM) was employed, estimated by restricted maximum likelihood taking the TUG, GARS, and BI measurements at each of the three visits as the response variable.

The models controlled statistically for the fixed effects of AGEs level, time (visit), gender, age, polypharmacy, dementia duration, cognition (MMSE), paratonia, chronic kidney disease (CKD), cardiovascular disease (CVD), cerebral vascular disease (CeVD), and diabetes mellitus (DM) (Rahmadi *et al.*, 2011). Participants were taken as random effects. Backward model selection was utilized to identify statistically significant explanatory variables. During this process, AGEs level and time were always retained in order to study the size of their effect.

To investigate change in mean over one year (between the last visit and baseline) on AGE levels and TUG, GARS, and BI, paired sample *t*-tests were performed. Pearson's *R* was calculated to investigate the association between change in AGE levels and change in the previously described variables. To further explore specific longitudinal effects, a linear regression was used where the change of the described scores between visit three and one was used as a response variable and changes of AGEs level and baseline characteristics (described above) as explanatory variables.

Data were analyzed using R version 3.2.0 and SPSS version 22, taking a *p*-value < 0.05 as statistically significant.

Results

From the 244 people with dementia approached to take part in the study, 87 were not included due to not satisfying the inclusion criteria; 13 participants withdrew informed consent prior to the baseline assessment. Finally, 144 participants were included at baseline. After one year, 26 participants (18%) were lost to follow-up: 11 deceased, while 15 were transferred to unknown addresses or became too ill to be reassessed (Figure 1). For comorbidity and medication use in 11% of the participants (*n* = 16), no information was accessible in the medical records (information derived from the PARAGE study (Drenth *et al.*, 2017)).

The baseline characteristics are summarized in Table 1.

Association between AGEs and mobility

Table 2 indicates that, after correction for age, polypharmacy, CKD, CVD, and MMSE, functional mobility (TUG) was significantly associated with the AGE levels ($\beta = 3.57$, *p* = 0.001, 95%CI: 1.43–5.73) and with the progression of dementia over a one-year time span ($\beta = 3.73$, *p* = 0.001, 95%CI: 1.46–5.91).

Association between AGEs and ADL

Table 3 indicates that, after removing covariates not being statistically significant, the AGE levels did not have a significant effect on ADL; however, the GARS (BADL/IADL) and BI were associated with the progression of dementia over one-year time span ($\beta = 2.58$, *p* < 0.001, 95%CI: 1.47–3.67, $\beta = 1.98$, *p* < 0.001, 95%CI: 0.79–3.17 and $\beta = -2.00$, *p* < 0.001, 95%CI: -2.58 to -1.42, respectively).

The one-year development of AGE levels and functional mobility and ADL (BADL/IADL) is presented in Table 4. From the 118 participants (82%) who completed this study, the longitudinal data over one year indicates that there was a significant increase in the overall AGE levels as well as TUG and GARS scores and a significant decrease in BI scores. Changes in functional performance (TUG, GARS, and BI) between baseline and visit three indicated no significant correlation with changes in the AGE level over one year. The linear regression models show that change in AGEs level is not predictive for changes

Table 1. Baseline characteristics

	TOTAL N = 144	
	FREQUENCY	RANGE MIN-MAX
Male, <i>n</i> (%)	63 (43.7%)	
Age, years	80.7 (7.7)	53–98
Dementia duration, months ^a	29.8 (35.9)	1–252
Co-morbidities, <i>n</i> ^a	1.18 (1.1)	0–4
AD, <i>n</i> (%) ^a	107 (83.6%)	
Mixed AD/VaD, <i>n</i> (%) ^a	21 (16.4%)	
AD or Mixed AD/VaD, <i>n</i> (%) ^b	16 (11.11%)	
CVD, <i>n</i> (%) ^a	41 (32.0%)	
CeVD (CVA, TIA), <i>n</i> (%) ^a	22 (17.2%)	
DM, <i>n</i> (%) ^a	37 (28.9%)	
Cancer, <i>n</i> (%) ^a	14 (11.0%)	
COPD, <i>n</i> (%) ^a	14 (11.0%)	
CKD, <i>n</i> (%) ^a	11 (8.6%)	
Systemic, <i>n</i> (%) ^a	8 (6.3%)	
Digestive tract, <i>n</i> (%) ^a	6 (4.7%)	
Polypharmacy (≥ 5 meds), <i>n</i> (%) ^a	71 (55.5%)	
MMSE, score 0–30	19.4 (5.4)	6–29
GDS, score 1–7	3.84 (1.0)	2–5
Paratonia, PAI Yes	60 (41.7%)	
TUG, seconds	17 (9.7)	7–65
GARS BADL, score 11–44	16.0 (5.7)	1–37
GARS IADL, score 7–28	16.8 (6.3)	7–28
GARS total, score 18–72	32.9 (10.7)	18–65
BI, score 0–20	16 (3.5)	6–20
AGE levels, SAF (AU)	2.8 (0.7)	0.4–4.9

Frequency data represent mean values (SD) unless indicated otherwise.

^aBased on GP medical files *n* = 128, ^bbased on chart diagnoses provided by day-care staff personnel for study inclusion.

CVD: Cardio Vascular disease, CeVD: Cerebral Vascular disease, CVA: Cerebral Vascular Accident, TIA: Transient Ischemic Attack, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, MMSE: Mini Mental State Exam, GDS: Global Deterioration Scale, TUG: Timed Up and Go, GARS: Groninger Activity Restriction Scale, BADL: Basic Activities Daily Living, IADL: Instrumental Activities Daily living BI: Barthel Index, AGE's: Advanced Glycation End-products, SAF: Skin AutoFluoresce (AGE reader) AU: Arbitrary Units i.e., the output units of the AGE reader.

in functional performance, not even after adjusting for baseline characteristics.

Discussion

Over a one-year time span, the AGE levels significantly increased and mobility, BADL and IADL performance decreased. This study shows that AGE levels are significantly associated with functional mobility, however, not with BADL or IADL in people experiencing early stage AD and mixed Alzheimer's/Vascular disease (AD/VaD).

Although change in AGE levels was not significantly related to change in functional mobility, mixed model analyses revealed a significant combined time and between participant effects of AGEs on functional mobility. Participants

with higher AGE levels scored higher on the TUG, indicating lower functional mobility. The encountered Beta effect means that, with every unit of AGE reader increase, the time to perform the TUG increases with 3.57 sec. The TUG measures functionality when transferring from sitting to standing, turning, and walking speed. A TUG score greater than 20 sec indicates mobility problems and slow walking speed that is associated with a wide range of adverse health consequences such as frailty, falls, disability, hospitalization, and institutionalization (Ries *et al.*, 2009). It is suggested that every decrease of 0.1 m/sec in walking speed already increases the risk of these negative health outcomes (Graham *et al.*, 2008). With a typical clinical AD duration of eight to ten years (Bird, 1993), extrapolating the Beta effect of 3.57 sec would become even more relevant.

Table 2. Association between AGEs and mobility (TUG) corrected for possible explanatory variables obtained after backward model selection

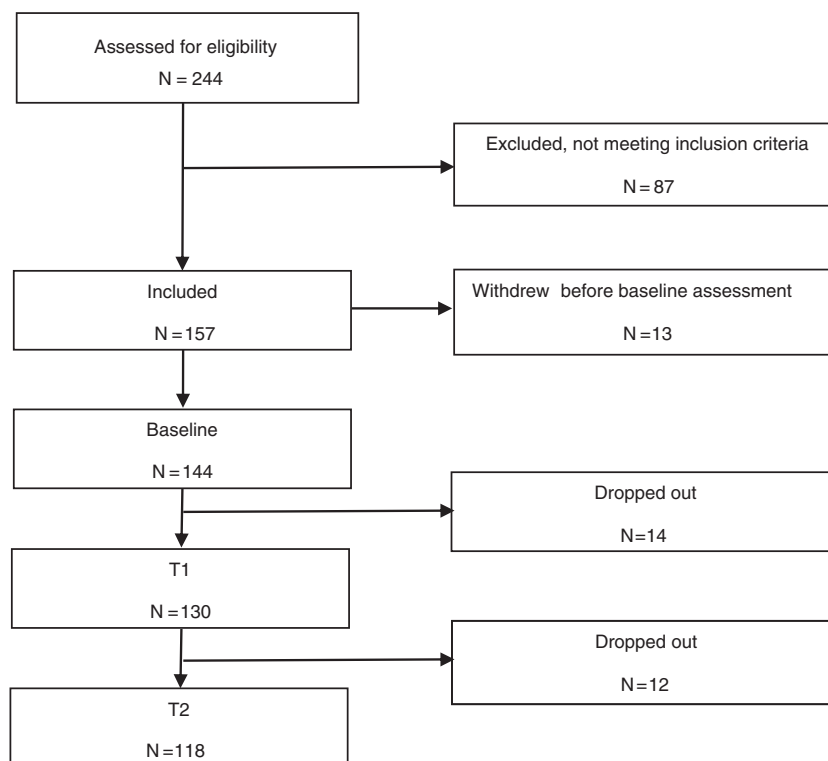
	MOBILITY (TUG)			
	ESTIMATE	P VALUE	95% CI	
			LOWER LIMIT	UPPER LIMIT
(Intercept)	− 14.33	0.196	− 35.59	6.90
Age	0.42	0.002	0.16	0.68
Polypharmacy	4.75	0.020	0.88	8.60
CKD	− 8.75	0.012	− 15.31	− 2.19
MMSE	− 0.76	<0.001	− 1.11	− 0.40
AGE levels	3.57	0.001	1.43	5.73
Visit2*	2.41	0.026	0.30	4.50
Visit3*	3.73	0.001	1.46	5.91

Response variable: Timed Up and Go (TUG) in seconds.

Explanatory variable: AGE levels (SAF) AU.

CKD: Chronic Kidney Disease, MMSE: Mini-Mental State Exam, AGE: Advanced Glycation End-product.

*Visit effects with respect to baseline (Visit1).

**Figure 1.** Study flow chart.

The result from this study is consistent with studies describing the effect of AGEs on the decline of walking abilities and contributes to the increasing evidence that decline in functional mobility can be attributed to the effects of AGEs on muscle tissue (Drenth *et al.*, 2016). The loss of skeletal muscle mass and weakness is an important contributor to functional decline. Both muscle weakness and walking impairment are prominent

characteristics of physical frailty (Sternberg *et al.*, 2011), suggesting that high AGEs level are a contributing factor to physical frailty. It remains ambiguous whether the association between high AGE levels and functional mobility decline exists because AGEs damage muscle tissue or whether loss of physical activity due to functional mobility decline influences AGEs accumulation. Future research is necessary to study this more in depth.

Table 3. Association between AGEs and ADL (GARS IADL and BADL and Barthel index), corrected for possible explanatory variables obtained after backward model selection

	GARS BADL				GARS IADL				BARTHEL INDEX			
	95% CI				95% CI				95% CI			
	ESTIMATE ^a	P VALUE	LOWER LIMIT	UPPER LIMIT	ESTIMATE ^b	P VALUE	LOWER LIMIT	UPPER LIMIT	ESTIMATE ^c	P VALUE	LOWER LIMIT	UPPER LIMIT
(Intercept)	12.63	<0.001	9.32	15.94	14.83	<0.001	11.51	18.16	23.27	<0.001	17.04	29.47
Age	–	–	–	–	–	–	–	–	–0.13	0.001	–0.21	–0.06
Polypharmacy	3.30	0.001	1.38	5.23	–	–	–	–	0.25	<0.001	0.14	0.35
AGE levels	0.46	0.404	–0.62	1.54	0.68	0.219	–0.41	1.77	–0.49	0.110	–1.08	0.11
Visit2*	2.12	<0.001	1.06	3.17	1.16	0.044	0.02	2.29	–1.01	<0.001	–1.55	–0.45
Visit3*	2.58	<0.001	1.47	3.67	1.98	0.001	0.79	3.17	–2.00	<0.001	–2.58	–1.42

^aResponse variable: Basic Activities Daily Living (BADL) Groninger Activity Restriction Scale (GARS).^bResponse variable: Instrumental Activities Daily living (IADL) Groninger Activity Restriction Scale (GARS).^cResponse variable: Barthel Index (BI).

Explanatory variable: AGE levels (SAF) AU.

MMSE: Mini-Mental State Exam, AGE: Advanced Glycation End-product.

*visit effects with respect to baseline (Visit1).

In accordance with the results of this study, it would be interesting to investigate whether decline in functional mobility can be attenuated by reducing AGEs levels. Excessive elevation of glucose concentration, such as in DM, most likely accelerates the glycation of proteins (Ahmed and Thornalley, 2007; Rahmadi *et al.*, 2011). Intensive glycaemic control may be a method to decrease AGEs formation. AGEs are not only produced endogenously, but are also spontaneously generated in standard diets (Magelhaes *et al.*, 2008). Therefore, dietary intake is a possible factor that can be influenced. In order to lower daily AGEs intake, it is suggested that foods rich in sugar and fat as well as those prepared by frying or grilling should be avoided (Puyvelde *et al.*, 2014). However, evidence of the harmful effects of long-term exposure to dietary AGEs is currently inconclusive (Puyvelde *et al.*, 2014). Additionally, regular physical activity has demonstrated a correlation with reduced glycation and AGE formation; however, the optimal exercise modalities still remain unclear (Magelhaes *et al.*, 2008). In addition, pharmacologic strategies to prevent AGE formation or AGE accumulation are being studied, but results show conflicting evidence and additional research is necessary (Nenna *et al.*, 2015).

An association between AGE levels and decline in ADL (BADL/IADL) was not determined. This is in contrast with a large cohort ($n = 3,373$) study by Whitson *et al.* that reported an association between serum AGE levels and the time to incident BADL disability in healthy participants over 14 years ($HR = 1.10$, 95%CI:1.05–1.15) (Whitson *et al.*, 2014). Although it is likely that impaired muscle function – through AGEs-induced muscle damage – can contribute to impaired BADL, the results from the current study did not confirm this in people with early stage dementia. Our sample size was possibly too small and a study duration of one year too brief to detect a decline in ADL, and/or the participants were less ADL independent at baseline. Further research with a longer follow up time is necessary to investigate if AGE levels are related to the deterioration of ADL during the course of AD, mixed dementia (AD/VaD), or other forms of dementia.

The strengths of this study are its longitudinal design with three assessments and that participating personnel were well trained in using the measurements. A study sample representative for this population was also created by including participants from rural and urban areas who were dispersed across the Netherlands. This study also has a number of limitations. First, the initial

Table 4. One-year development of AGE levels and mobility and ADL

	VISIT 1		VISIT 3		P VALUE VISIT				
	FREQUENCY	RANGE	FREQUENCY	RANGE	3-VISIT 1	R	P VALUE	BETA	P VALUE
AGE levels	2.8 (0.7)	0.4–4.9	3.0 (0.7)	1.6–5.3	<0.001	–	–	–	–
TUG	17 (9.7)	7–65	20 (15)	6–103	<0.001	0.002	0.984	–1.44	0.487
GARS BADL	16.1 (5.7)	1–37	18.3 (6.9)	11–39	<0.001	0.053	0.569	–0.81	0.428
GARS IADL	16.8 (6.3)	7–28	18.6 (6.7)	7–28	<0.001	0.053	0.570	0.18	0.896
Barthel index	16 (3.5)	6–20	14.2 (4.5)	1–20	<0.001	0.011	0.908	0.86	0.186

Frequency data represent mean values (SD) unless indicated otherwise.

TUG: Timed Up and Go, GARS: Groninger Activity Restriction Scale, BADL: Basic Activities Daily Living, IADL: Instrumental Activities Daily living, and AGE: Advanced Glycation End-product.

R: Pearson Correlation coefficient between change (delta visit 3 visit 1) in AGE levels and change (delta visit 3 visit 1) TUG, GARS, and BI scores.

Beta: Linear regression model between change (delta visit 3 visit 1) in AGE levels and change (delta visit 3 visit 1) TUG, GARS, and BI scores.

number of 152 participants from our *a priori* sample size calculation could not be included. However, the study still comprised a reasonable number of 144 participants for baseline and 118 for follow up analysis. Second, due to the limitation of the AGE reader, it was not possible to indicate what types of AGEs (e.g. crosslinking or non-crosslinking) are responsible for our findings. Future fundamental research is necessary to further explore this. Finally, the follow-up period of one year is possibly insufficient for detecting an association between changes in AGE levels and change in functional performance over time. Prolonging the study over several years and in a larger cohort could result in improved insight in the long-term effects of AGEs on functional performance. Further longitudinal studies over several years are needed to investigate a causal relationship.

In conclusion this study indicates that high AGE levels could be a contributing factor to the decline in functional mobility in addition to the progressive brain pathology, but lacks evidence for an association with ADL decline in people with early stage AD or mixed dementia. This result contributes to the increasing evidence that high AGE levels could affect functional mobility in the aging population. Future research is necessary into interventions such as physical activity programs and dietary advice targeting AGE accumulation possibly in combination with pharmacologic strategies to attenuate functional decline in those experiencing dementia.

Conflict of interest

None.

Description of authors' roles

H. Drenth is the first author and was responsible for the conception and design, the acquisition, analysis and interpretation of data, and drafting the manuscript. S. Zuidema has been involved in the conception and design and has been involved in reviewing the manuscript critically for important intellectual content. W. Krijnen was involved in the data analysis and reviewing the manuscript critically for important intellectual content. I. Bautmans has been involved in reviewing and revising the manuscript critically for important intellectual content. C. van der Schans has been involved in revising the manuscript critically for important intellectual content. H. Hobbelen has been involved in the conception and design, reviewing the manuscript critically for important intellectual content, and has given final approval of the version to be published. All authors read and approved the final manuscript.

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